Arylidene Derivatives as Synthons in Heterocyclic Synthesis

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Abstract
This review describes the synthetic procedures for the preparation of arylideneacetophenones, arylidenecycloalkanones, 2-arylidene-1-indanones, 2-arylidene-1-tetralones, 2-arylidene-1-benzosuberones, aurones, 1-thiaaurones, 3-arylidene-4-chromanones, 3-arylideneflavanones, 3-arylidene-1-thioflavanones, arylidenemalononitriles, diethyl arylidenemalonates, ethyl arylidenecyanoacetates, arylidenecyanoacetamides, 5-arylidene derivatives of barbituric and thioarbituric acids, arylidene derivatives of Meldrum’s acid and arylidene derivatives of dimedone. Also, it demonstrates the reactivity of these arylidene derivatives in heterocyclic synthesis with emphasis on the most recent findings. Some of these are the α,β-enones, víz. aurones and 3-arylidene-4-chromanones belong to the natural products. The others are synthetic substances which are convenient and important intermediates for the synthesis of a variety of useful and novel heterocyclic systems.

Keywords
Arylidenes, Synthesis, Reactions, Heterocycles

1. Introduction
The chemistry of different arylidene compounds has generated intensive scientific studies throughout the world. Especial interest has been focused on the synthesis and pharmacological activities of different arylidene compounds. They are versatile synthons so that a variety of novel heterocycles with good pharmaceutical profiles can be designed. Those arylidenes are usually prepared through Knoevenagel condensations of aldehydes with active methylene compounds, they are usually base [1], Lewis acid [2], or surfactant-catalyzed [3]; thus, create much wastes. Recently, there was an interest in so-called solvent-free [4] [5] Knoevenagel condensations on solid supports that were promoted by infrared [6] or microwave irradiation [7] [8]. Unfortunately, the latter techniques...
require solvents for the extraction from the solid supports as well as for the preparation of the initial adsorbates, and do not yield pure products. Thus, further solvents are required for purifying the workup. Even catalyst-free Knoevenagel reactions in water could not reach quantitative yields [9]-[11]. This research deals with the various methods of preparation of arylideneacetophenones, arylideneacycloalkanones, 2-arylidene-1-indanones, 2-arylidene-1-tetralones, 2-arylidene-1-benzosuberones, aurones, 1-thiaurones, 3-arylidene-4-chromanones, 3-arylidene-1-thio-4-chromanones, 3-arylideneflavanones, 3-arylidene-1-thioflavanones, arylideneanilines, arylidene-malononitriles, diethyl arylidenemalonates, ethyl arylidenecyanoacetates, arylidenecyanoacetamides, 5-arylidene derivatives of barbituric and thiobarbituric acids, arylidene derivatives of Meldrum’s acid and arylidene derivatives of dimedone as well as their utilization in heterocyclic synthesis.

2. Synthesis

2.1. Synthesis of Arylideneacetophenone Derivatives (Chalcones)

Different methods are available for the preparation of chalcones [12]-[14]. The most convenient method is the Claisen-Schimdt condensation of equimolar quantities of arylmethylketones with aryl aldehydes in the presence of aqueous alcoholic alkali [15]-[25]. Chalcones are used to synthesize several derivatives like cyanopyridines, pyrazolines, isoxazoles, and pyrimidines having different heterocyclic ring systems [26]-[29].

2.1.1. Various Condensing Agents Have Been Used in the Synthesis of Chalcones

1) Alkali

Alkalis are the most widely used condensing agents for the synthesis of chalcones. They are used as an aqueous alcoholic solution of suitable concentration viz. 30%, 40%, 50% and 70% [15]-[25].

2) Acids

Methanolic solution of dry hydrochloric acid gas at 0°C was used for the synthesis of chalcones from aromatic ketones and aldehydes [26] [27]. In addition, concentrated sulfuric acid in acetic acid was used as a condensing agent in the synthesis of chalcones [28].

3) Other Condensing Agents

Raval and Shah [29] used phosphorous oxychloride as a condensing agent to synthesize chalcones. In addition, Szell and Sipos [30] condensed 2-hydroxy-5-nitroacetophenone with benzaldehyde using anhydrous AlCl₃. Besides the above, other condensing agents have been used in the synthesis of chalcones; namely, amino acids [31], an aqueous solution of borax [32], perchloric acid [33], piperidine [34], boron trifloride [35], alkali metal alkoxides [36], magnesium tert-butoxide [37], and thionyl chloride [38]. In recent years, microwave assisted solid support solvent-free organic synthesis have attracted the attention as they offer several advantages such as simple procedure, fast reaction rate, mild reaction conditions, eco-friendly and improved yields as compared to conventional methods [39] [40].

2.1.2. Mechanism

The following mechanisms have been suggested for the synthesis of chalcones:

1) Base catalyzed reaction (Scheme 1) [21] [41].
2) Acid catalyzed reaction (Scheme 2) [42].

2.1.3. Reactivity of Chalcone Derivatives

The chalcones 1 are useful intermediates for the synthesis of a variety of heterocyclic compounds. Isoxazoles 2 are prepared by the reaction of chalcones 1 with hydroxylamine hydrochloride and sodium acetate [43] (Scheme 3). Treatment of chalcones 1 with guanidine hydrochloride in the presence of alkali afforded 2-aminopyrimidines 3 [44] (Scheme 3). Thiazines 4 and oxazines 5 can be synthesized by reaction of chalcones 1 with thiourea and urea, respectively [45] (Scheme 3). Pyrazoles 6, 7 are obtained through the reaction of chalcones 1 with hydrazine hydrate and phenyl hydrazine derivatives, respectively [46]-[49] (Scheme 3). Furthermore, reaction of hydrazine hydrate with 1 in the presence of different aliphatic acids resulted in the formation of pyrazole derivatives containing N-acyl moiety 8a-e [49] [50] (Scheme 3). Condensation of chalcones 1 with malononitrile and ammonium acetate yields 2-amino-3-cyanopyridines 9 [49] [51] (Scheme 3). On the other hand, reaction of 1 with malononitrile in refluxing methanol or ethanol and in the presence of freshly prepared sodium alkoxide solution yielded 3-cyanopyridines 10 [52] (Scheme 3). Reaction of cyanopyridines 10 with hydrazine hydrate
Scheme 1. Mechanism of base catalyzed condensation of aromatic ketones with aldehydes.

Scheme 2. Mechanism of acid catalyzed condensation of aromatic ketones with aldehydes.
Scheme 3. Preparation of compounds 2-10 and 12-24.

using Lewis acid (1.0 equivalent of BF₃·Et₂O) in refluxing ethanol under anhydrous conditions afforded 1H-pyrazolo[3,4-b]pyridines 11 in very good yields and short reaction time [52] (Scheme 4). Similarly, treatment of 1 with ethyl cyanoacetate in absolute ethanol and in the presence of ammonium acetate afforded cyanopyridine derivatives 12 [49] (Scheme 3). Reaction of 1 with cyclohexane-1,3-diones produced 2,4-diaryl-5-oxo-5,6,7,8-tetrahydro-2-chromenes 13a, b. [53] Similarly, acetoacetanilide and acetylcetone reacted with chalcones 1 to afford cyclohexenone derivatives 14 and 15, respectively [49] (Scheme 3). Epoxidation of chalcones 1 with urea-hydrogen peroxide (UHP) under ultrasound irradiation gave oxirane derivatives 16 [54] (Scheme 3). Reaction of 1 with semicarbazide hydrochloride in glacial acetic acid/dioxane afforded pyrazoline-1-carboxamides 17 [55] (Scheme 3). The barbitones 18 are obtained upon condensation of chalcones 1 with barbituric acid [49] [56] [57] (Scheme 3). Treating 1 with 4,5-diaminopyrimidine gave [1,4]diazepine derivatives 19 [58] (Scheme 3). Condensation of chalcones 1 with 2-aminothiophenol afforded [1,4]benzothiazepines 20 [59] (Scheme 3). Tetrahydro-1H-azepines 21 were synthesized via reaction of 1 with ethylenediamine [60] (Scheme 3). Reaction of chalcones 1 with cyclohexanone in benzene in the presence of sodium hydroxide and a catalytic amount of
tributyl benzyl ammonium chloride (TBBAC) at room temperature afforded 2-(1-oxo-1,3-diarylpropan-2-yl) cyclohexanones 22 [61] [62] (Scheme 3). Furthermore, reaction of 1 with isonicotinoyl hydrazide in refluxing ethanol gave N-isonicotinoyl-3,5-diarylpyrazolines 23 (Scheme 3) [49]. Reaction of 1 with methyl acetoacetate or ethyl acetoacetate in refluxing ethanol and in the presence of catalytic amounts of piperidine and basic alumina afforded 4,6-diaryl-2-oxocyclohex-3-ene-carboxylates 24a, b [49] [63] (Scheme 3). Condensation of cyclohexene-carboxylates 24a, b with hydrazine hydrate produced 4,6-diaryl-3-oxo-2,3,4,5-tetrahydroindazoles 25 [49] (Scheme 5).

2.2. Synthesis of Arylidenecycloalkanone Derivatives

Arylidenecycloalkanones are frequently used α,β-unsaturated ketones. Their synthesis is based on the reaction of the appropriate cyclic ketone with aldehydes, through aldol condensation reaction. Several reports exist for their synthesis [64]-[69], involving the use of organic and inorganic bases, metal catalysts, different types of Friedel-Crafts catalysts and trichloro-1,3,5-triazine (TCT). A more convenient method used solid potassium hydroxide [70] [71] or sodium hydroxide [72] as a catalyst for the condensation of different aldehydes with cycloalkanones in ethanol and resulted in α,α'-bis(substituted benzylidene)cycloalkanones 26 and 27 in good yields. This method is economical and eco-friendly as neither any byproduct was formed nor any toxic material was used during the synthesis, and the reactions were carried out at ambient temperature. In addition, the same condensation was carried out in refluxing ethanol and in the presence of a catalytic amount of ammonium chloride to afford α,α'-bis(arylidene)cycloalkanones [73]. Moreover, a simple and efficient procedure for the synthesis of α,α'-bis(arylidene)cycloalkanones has been developed using N-bromosuccinimide (NBS) as a catalyst under mild reaction conditions [74]. Recently, a simple, improved and solvent-free synthesis of 26 and 27 was performed using activated barium hydroxide and grinding three to five minutes at room temperature [75].

Reaction of cyclopentanone with substituted benzaldehydes (1:2 molar ratio) in alcoholic alkali solution produced α,α'-bis(substituted benzylidene)cyclopentanones 26 (Scheme 6) [76] [77].

Cyclohexanone was reacted with substituted benzaldehydes under alkaline reaction conditions (1:2 molar ratio) to afford α,α'-bis(substituted benzylidene)cyclohexanones 27 which could be easily separated (Scheme 7) [76]-[82]. The same condensation was carried out using amino-functionalized ionic liquid, 1-aminoethyl-3-methyl tetrafluoroborate ([2-aemim][BF₄]) as solvent and catalyst [83]. In addition, Brønsted acid-surfactant catalyst was utilized for synthesis of α,α'-bis(substituted benzylidene)cyclohexanones in aqueous media [84].

In addition, α,α'-bis(substituted benzylidene)cycloalkanones 26 and 27 could be obtained by refluxing 1,1-diacetates and cycloalkanones in tetrahydrofuran (THF) and in the presence of Samarium (III) Triiodide (SmI₃) as a catalyst (Scheme 8) [85].

Cyclohexylphenyl methanols 28 were prepared by D-glucosamine catalyzed aldol reaction of cyclohexanone with substituted benzaldehydes (Scheme 9) [86].

3,5-Dibenzylidene-4H-pyran-4-ones (30, X = O) and 3,5-dibenzylidene-4H-1-thiopyran-4-ones (30, X = S) were synthesized via reaction of tetrahydro-4H-pyran-4-one (29, X = O) or tetrahydro-4H-1-thiopyran-4-one (29, X = S) with substituted benzaldehydes either under alkaline [87]-[90] or acidic [91] [92] reaction conditions (Scheme 10).
2.3. Synthesis of 2-Arylidene-1-Indanone Derivatives

2-Arylidene-1-indanones 32 are important intermediates for the synthesis of a wide variety of heterocyclic ring systems. For this reason, it is useful to have simple and convenient procedures for their preparation. Most of the utilized syntheses are based on the condensation of 1-indanones 31 with aldehydes in the presence of a catalyst to afford 2-arylidene-1-indanones 32 (Scheme 11).

In most cases sodium or potassium hydroxide is used as a catalyst [93]-[99] and 2-arylidene-1-indanones 32 are obtained in good yields. In addition, various inorganic acids, *viz.* sulfuric, phosphoric or hydrochloric acids were used as catalysts to prepare 32 [100]-[105]. It is worth mentioning that acetic anhydride was used to facilitate the condensation of indanones with substituted benzaldehydes [106]. Basavaiah and Reddy [107] have introduced a simple one-pot procedure for the preparation of 2-arylidene-1-indanones 32 starting from *tert*-butyl 3-aryl-3-hydroxy-2-methylene propanoate 33, which was allowed to react with a catalytic amount of concen-
trated sulfuric acid in benzene followed by reaction of the intermediates formed with trifluoroacetic anhydride (TFAA) in methylene chloride to afford 32 (Scheme 12).

**Reactivity of 2-Arylidene-1-Indanone Derivatives**

The synthesis of indeno[1,2-c]pyrazoles 34 was accomplished via reaction of 2-arylidene-1-indanones 32 with phenylsulfonylhydrazide in an inert solvent such as aromatic hydrocarbon and in the presence of a catalytic amount of acid [108] (Scheme 13). The [3 + 2] cycloaddition reactions of 2-arylideneindanones 32 with the arylnitrite oxides generated in situ from arylhydroxyaminoyl chlorides 35 and triethylamine led to the formation of the spiro derivatives 36 [109] (Scheme 14).

### 2.4. Synthesis of 2-Arylidene-1-Tetralone Derivatives

2-Arylidene-1-tetralones 38 are useful intermediates for the synthesis of polycyclic ring systems. Several synthetic methods have been developed for their preparation. The majority of compounds 38 have been synthesized by the condensation of 1-tetralones 37 with aromatic aldehydes in aqueous alcoholic solution of sodium or potassium hydroxide [94] [110]-[122]. Piperidine is another alkaline catalyst which has also been used to obtain 2-arylidene-1-tetralones 38 [108] [123]-[126]. In addition, acidic catalysts such as sulfuric, phosphoric and hydrochloric acids were utilized for this condensation [127]-[129] (Scheme 15).

**Reactivity of 2-Arylidene-1-Tetralone Derivatives**

The naphtho[1,2-c]pyrazole derivatives 39 were prepared via reaction of 2-arylidene-1-tetralones 38 with phenylsulfonylhydrazide in an inert solvent such as aromatic hydrocarbon and in the presence of a catalytic amount of acid [108] (Scheme 16).

The reaction of 38 with the bicyclic carbonyl ylide 41 generated from the α-diazo ketone 40 in the presence of Rh₂(OAc)₄, afforded the spirodioxa ring systems 42 [130] (Scheme 17).
Moreover, the preparation of benzo[g]pyrazolo[3,4-b]quinolines 43 was accomplished via cyclocondensation reaction of 38 with aminopyrazoles under solvent-free conditions [131] (Scheme 18).

Treatment of 38 with potassium isothiocyanate gave 2-[aryl(isothiocyanato)methyl]-3,4-dihydronaphthalen-1(2H)-ones 44. Reaction of 44 with primary aromatic amines gave 4-aryl-1-(substituted phenyl)-1,4,5,6-terahydrobenzol[h]quinazoline-2-thiols 45 [129] (Scheme 19).

Dispiropyrrolidinyl derivatives, 1',2',3',4'-tetrahydronaphthalen-1'-one-spiro[3'.3]-4-aryl-N-methylpyrrolidine-2-spiro-2''-acenaphthen-1''-ones 48 were obtained through reaction of 2-arylidene-1-tetralones 38, acenaphthylenquinone 46 and sarcosine 47 in aqueous methanol [132] (Scheme 20).

Furthermore, 1',2',3',4'-tetrahydronaphthalen-1'-one-spiro[2'.3]-[4-aryl]pyrrolidine-spiro-[2.2'']oxindoles 50 were synthesized via reaction of 2-arylidene-1-tetralones 38, isatin (49) and benzylamine in dry acetonitrile [132] (Scheme 21).

A new method to prepare benzo[c]xanthones 51 was reported by the ultraviolet radiation-mediated tandem reaction through irradiating a solution of 2-benzylidene-1-tetralones 38 in acetonitrile with ultraviolet light (500 W middle-pressure Hg) [133] (Scheme 22).

2.5. Synthesis of 2-Arylidene-1-Benzosuberone Derivatives

2-Arylidene-1-benzosuberones 53 were synthesized by the condensation of 1-benzosuberone 52 with aromatic aldehydes using alkaline [96] [121] [134] [135] or acidic [136] catalysts (Scheme 23).

2.6. Synthesis of Aurone Derivatives

Aurones 55 are the oxa analogues of the 2-arylidene-1-indanones 32, different procedures were adopted for their
Scheme 18. Preparation of compounds 43.

Scheme 19. Preparation of compounds 45.

Scheme 20. Preparation of compounds 48.

Scheme 21. Preparation of compounds 50.

Scheme 22. Preparation of compounds 51.
preparation. First, the Algar-Flynn-Oyamada reaction based on the oxidative cyclization of 2'-hydroxychalcones, where aurone is one of the products formed during preparation of 2'-hydroxychalcone [137]-[139]. Another procedure described by Donnelly and co-workers [140] [141] is based on bromomethylation of chalcones and 2'-acetoxychalcones followed by ring closure of the bromodihydro analogues providing aurones 55. However, none of these procedures can be considered as a rational method for the synthesis of aurones.

The most common synthetic procedures for aurones 55 are based on the condensation of coumaran-3-ones 54 with substituted benzaldehydes in the presence of a catalyst. As catalyst, sodium hydroxide [142] [143], potassium hydroxide [144], anhydrous sodium acetate [145], sulfuric [145], hydrochloric [146], and phosphoric acids [147] were used for this condensation (Scheme 24). Farkas et al. [148] [149] performed the condensation of the appropriate coumaran-3-one 54 with substituted benzaldehydes in refluxing acetic anhydride to obtain aurones 55.

Another synthetic procedure was developed for the preparation of aurones 55 through cyclization of 1-(2-hydroxyphenyl)-3-(substituted phenyl)prop-2-en-1-ones 56 in methanol and in the presence of a catalytic amount of silver nitrate [151] (Scheme 25).

In addition, other synthetic procedures were adopted for the preparation of aurones 55 through cyclization of 56 using mercuric acetate in pyridine [152] [153], mercuric acetate in polyethylene glycol (PEG-400) [154], mercuric acetate in dimethyl sulfoxide (DMSO) [155], and cupric bromide in DMSO [152] (Scheme 25).
Mechanism of Cyclization Using Mercuric Acetate in Pyridine [152]
The mechanism of cyclization of 56 into aurone derivatives 55 is illustrated in Scheme 26.

Furthermore, gold-catalyzed cyclization of alkynol derivatives 57 has become an efficient tool in the synthesis of aurones 55 and provided the best results under mild reaction conditions and excellent selectivities, avoiding the formation of flavones as byproducts [156] [157] (Scheme 27).

2.7. Synthesis of 1-Thioaurone Derivatives
1-Thioaurones 59 are synthetic thio analogues of the naturally-occurring aurones, their synthesis has already been published [158]-[162]. Condensation of 1-thiocoumaran-3-ones 58 with aromatic aldehydes in the presence of phosphoric acid [147] or piperidine [159] afforded 59. In addition, the same reaction was carried out in THF and in the presence of 1.5 equivalents of lithium diisopropylamide (LDA) at −10°C [163] (Scheme 28).

Moreover, a convenient one-step synthesis has been published [161], whereas, equimolar amounts of (2-methylthio)benzoic acid derivatives 60 and aromatic aldehydes were allowed to react with 2.0 equivalents of LDA in THF at 0°C to yield 1-thioaurones 59 (Scheme 29).

In 2010, Boughaleb et al. [162] described new synthetic pathway for the preparation of 1-thioaurones 59 (Scheme 30).

Reactivity of Aurone and 1-Thioaurone Derivatives
Reaction of 55 or 59 with 2-aminothiophenol in ethanol and in the presence of sodium ethoxide gave the spiro compounds 61a, b. By the way of contrast, the 6,12-dihydrobenzofuro[2,3-c][1,5]benzothiazepines 62a and the
6,12-dihydrobenzothieno[2,3-c][1,5]benzothiazepines 62b were obtained in good yields via heating 55 or 59, respectively with 2-aminothiophenol in polyphosphoric acid (PPA) under nitrogen. Treatment of 62a, b with 2-chloroethyl-N,N-dimethylammonium chloride and potassium carbonate in ethyl acetate produced the annulated benzofuran and benzothiophene derivatives 63a, b. The tetracyclic derivatives 62a, b were deprotonated with sodium hydride in DMF to afford compounds 64a, b [164] (Scheme 31).

Reaction of aurones 55 with hydrazine hydrate in ethanol gave the benzofuro[3,2-c]pyrazole derivatives 65. Refluxing aurones 55 with phenyl hydrazine in glacial acetic acid gave the benzofuro[3,2-c]pyrazole derivatives 66. In addition, benzofuro[3,2-c]isoxazole derivatives 67 were synthesized by the reaction of aurones 55 with hydroxylamine hydrochloride in alcoholic solution of potassium hydroxide. Furthermore, benzofuro[2,3-c]pyridine derivatives 68 were obtained through reaction of aurones 55 with acetyl chloride in alcoholic solution of potassium hydroxide. Finally, benzofuro[3,2-d]pyrimidine derivatives 69 were synthesized via reaction of aurones 55 with urea or thiourea in alcoholic solution of potassium hydroxide [165] (Scheme 32).

2.8. Synthesis of 3-Arylidene-4-Chromanone Derivatives

The synthesis and chemical transformation of 3-arylidene-4-chromanones and related compounds received much attention due to the abundance of this moiety in many natural products and biologically active substances [166]-[169]. Thiochromones are synthetic compounds and some of their derivatives are reported to have medicinal uses [170] [171]. Current literature showed that there has been an increasing trend towards the synthesis of heterocycles containing these two ring systems [172].

The synthesis of 3-arylidene-4-chromanones 71 is based on the condensation of 4-chromanones 70 with aromatic aldehydes in the presence of a catalyst (Scheme 33). Acid-catalyzed condensation (H₂SO₄, H₃PO₄ or HCl) of the two components was accomplished [173]-[180]. In addition, Farkas et al. [181]-[183] performed the same reaction in hot acetic anhydride, which is a very simple and convenient method, but sometimes it requires a prolonged time. Another procedure used for the synthesis of 71 is the base catalyzed condensation of 4-chromanones 70 with aromatic aldehydes using sodium hydroxide [184], sodium methoxide [185], anhydrous potassium acetate [186], piperidine [187]-[189], or pyrrolidine [190]. A new synthetic method for 71 was through...
Scheme 31. Preparation of compounds 61-64.

Scheme 32. Preparation of compounds 65-69.
condensation of different aromatic aldehydes with 4-chromanones 70 using amberlyst-15 as a catalyst under microwave irradiation in solvent-free conditions [191]. However, it should be mentioned that in case of using piperidine as a catalyst, an exo-endo double bond migration takes place if the aldehyde has strong electron-drawing substituents [188] [192]. In such a case, 3-arylmethyl-4-chromenone (homoisoflavone) 72 is the product instead of the expected 3-arylidene-4-chromanone 71 (Scheme 34). Basavaiah et al. [107] [193] synthesized 3-arylidene-4-chromanones 71 by ring closure of the acrylic acid derivatives 73 with TFAA in methylene chloride (Scheme 35).

**Reactivity of 3-Arylidene-4-Chromanone Derivatives**

Refluxing a solution of 3-arylidene-4-chromanone 71, isatin (49) and sarcosine (74) afforded 4-aryl-N- methyl-spiro[2.3'][2-oxoindoline]-spiro[3.3''](substituted 4-chromanone)pyrrolidines 75 [194] (Scheme 36). Whereas, refluxing a solution of 71, isatin (49) and L-proline (76) in aqueous methanol gave 4-aryl-spiro[2.3'][2-oxoindoline]-spiro[3.3''](substituted 4-chromanone)hexahydropyrrolizines 77. The reaction proceeded via formation of an azomethine ylide which readily undergoes 1,3-dipolar cycloaddition reaction with 3-arylidene-4-chromanones to give a single cycloadduct [194] (Scheme 36).

### 2.9. Synthesis of 3-Arylidene-1-Thio-4-Chromanone Derivatives

The synthesis of 3-arylidene-1-thio-4-chromanones 79 is based on the condensation of 1-thio-4-chromanones 78 with aromatic aldehydes under acidic conditions [195]-[199]. The same condensation was accomplished using piperidine as a catalyst [187]-[189], or amberlyst-15 under microwave irradiation [191] (Scheme 37). As described for the condensation of 4-chromanone 70 with aromatic aldehydes [187] [188], in case of aromatic aldehydes bearing strongly electron-drawing substituents, an exo-endo double bond transposition also takes place, resulting in the formation of 3-arylmethyl-1-thio-4-chromenones 80 instead of 3-arylidene-1-thio-4-chromanones 79 [188] (Scheme 38).

### 2.10. Synthesis of 3-Arylideneflavanone Derivatives

3-Arylideneflavanones (flavindognides) 82 are well known flavanone derivatives. They were first synthesized by Katschalowsky and von Kostanecki in 1904 [200]. They were also synthesized by the acid-catalyzed condensation of different aromatic aldehydes with 4-chromanones 70 using amberlyst-15 as a catalyst under microwave irradiation in solvent-free conditions [191]. However, it should be mentioned that in case of using piperidine as a catalyst, an exo-endo double bond migration takes place if the aldehyde has strong electron-drawing substituents [188] [192]. In such a case, 3-arylmethyl-4-chromenone (homoisoflavone) 72 is the product instead of the expected 3-arylidene-4-chromanone 71 (Scheme 34). Basavaiah et al. [107] [193] synthesized 3-arylidene-4-chromanones 71 by ring closure of the acrylic acid derivatives 73 with TFAA in methylene chloride (Scheme 35).

**Reactivity of 3-Arylidene-4-Chromanone Derivatives**

Refluxing a solution of 3-arylidene-4-chromanone 71, isatin (49) and sarcosine (74) afforded 4-aryl-N-methyl-spiro[2.3'][2-oxoindoline]-spiro[3.3''](substituted 4-chromanone)pyrrolidines 75 [194] (Scheme 36). Whereas, refluxing a solution of 71, isatin (49) and L-proline (76) in aqueous methanol gave 4-aryl-spiro[2.3'][2-oxoindoline]-spiro[3.3''](substituted 4-chromanone)hexahydropyrrolizines 77. The reaction proceeded via formation of an azomethine ylide which readily undergoes 1,3-dipolar cycloaddition reaction with 3-arylidene-4-chromanones to give a single cycloadduct [194] (Scheme 36).

### 2.9. Synthesis of 3-Arylidene-1-Thio-4-Chromanone Derivatives

The synthesis of 3-arylidene-1-thio-4-chromanones 79 is based on the condensation of 1-thio-4-chromanones 78 with aromatic aldehydes under acidic conditions [195]-[199]. The same condensation was accomplished using piperidine as a catalyst [187]-[189], or amberlyst-15 under microwave irradiation [191] (Scheme 37). As described for the condensation of 4-chromanone 70 with aromatic aldehydes [187] [188], in case of aromatic aldehydes bearing strongly electron-drawing substituents, an exo-endo double bond transposition also takes place, resulting in the formation of 3-arylmethyl-1-thio-4-chromenones 80 instead of 3-arylidene-1-thio-4-chromanones 79 [188] (Scheme 38).
of flavanones \(81\) with aromatic aldehydes \([200]-[204]\) (Scheme 39). In addition, glycine was described as a catalyst for this condensation \([205]\). It was reported that in some cases the base catalyzed condensation of hydroxyacetophenone with benzaldehyde gave 3-benzylideneflavanone as a coproduct of the corresponding hydroxychalcone \([206]-[208]\). Furthermore, the synthesis of \(82\) via base-catalyzed condensation of flavanone \(81\) with aromatic aldehydes was reported \([189]\) \([209]\). It is worth mentioning that if aldehydes with strong electron-withdrawing substituents are used, 3-arylmethylflavones \(83\) are obtained instead of 3-arylideneflavanones \(82\) \([210]\) (Scheme 40). 3-Arylmethylflavones \(83\) were also obtained via treatment of \(82\) with pyridinium chlorochromate (PCC) (5.0 equivalent) in DMF \([211]\) (Scheme 41).

### 2.11. Synthesis of 3-Arylidene-1-Thioflavanone Derivatives

3-Arylidene-1-thioflavanones \(85\) were synthesized by the acid-catalyzed condensation of 1-thioflavanones \(84\) with aromatic aldehydes \([212]\) \([213]\) (Scheme 42). Also, base catalyzed condensation of thioflavanones \(84\) with aromatic aldehydes using piperidine was reported \([214]\). However, this procedure can be used only for the synthesis of 3-arylidene-1-thioflavanones substituted with electron-donating or slightly electron-withdrawing substituents in the arylidene moiety. When aromatic aldehydes substituted with strongly electron-withdrawing substituents were used, 3-arylmethyl-1-thioflavones \(86\) were obtained \([214]\) \([215]\) (Scheme 43).

### Reactivity of 3-Arylidene-1-Thioflavanone Derivatives

Reaction of 3-arylidene-1-thioflavanones \(85\) with sodium oxychloride and hydrogen peroxide gave 3-arylidene-
Scheme 39. Preparation of compounds 82 through condensation of flavanones 81 with aromatic aldehydes substituted with electron-donating groups.

Scheme 40. Preparation of compounds 83 through condensation of flavanones 81 with aromatic aldehydes substituted with strong electron-withdrawing groups.

Scheme 41. Preparation of compounds 83 through treatment of 3-arylideneflavanones 82 with pyridinium chlorochromate (PCC).

Scheme 42. Preparation of compounds 85 through condensation of 1-thioflavanones 84 with aromatic aldehydes substituted with electron-donating groups.

Scheme 43. Preparation of compounds 86 through condensation of 1-thioflavanones 84 with aromatic aldehydes substituted with strong electron-withdrawing groups.
1-thioflavanone epoxides [87]. Reaction of epoxide derivatives [87] with dimethyldioxirane (DMD) yielded the sulfoxide and sulfone derivatives [88] and [89] (Scheme 44).

2.12. Synthesis of Arylideneaniline Derivatives (Schiff Bases)

Schiff bases are typically formed by the condensation of primary amines with aldehydes. Schiff bases are important intermediates for the synthesis of various bioactive compounds. Literature survey revealed that these compounds have been associated with diverse chemotherapeutic activities, including antimalarial [217], anticancer [218], antibacterial [219], antifungal [220], antitubercular [221], anti-inflammatory [222], antimicrobial [222] and antiviral [223] activities. On the other hand, they are fundamental materials for the synthesis of various Schiff base ligands which are used as chiral auxiliaries in asymmetric synthesis [224]. Metal complex Schiff bases have also been used in oxidation reactions [225].

2.12.1. Various Reaction Conditions Have Been Used in the Synthesis of Schiff Bases

Schiff bases are compounds containing an azomethine group (-C=NH-). They are usually formed by condensation of primary amines with carbonyl compounds according to the following equation [226]: R-NH₂ + R′-CHO → R-N = CH-R′ + H₂O, where R, R′ may be an aliphatic or aromatic group. Schiff bases of aromatic aldehydes have an effective conjugated system and are more stable [227]. They are prepared under various reaction conditions, the use of organic solvents such as THF and 1,2-dichloroethane (DCE) was reported [228]. The reaction was also carried out in ethanol at room temperature [229] [230], in refluxing ethanol [231], in refluxing ethanol and in the presence of a catalytic amount of anhydrous magnesium sulfate [238], using DCM and a catalytic amount of neutral alumina under microwave irradiation [238], under solvent-free conditions in the presence of lemon juice as natural acid catalyst [239], in refluxing methanol and in the presence of a catalytic amount of anhydrous zinc chloride [237], in refluxing benzene [238], in dichloromethane (DCM) at room temperature and in the presence of anhydrous magnesium sulfate [238], using DCM and a catalytic amount of neutral alumina under microwave irradiation [238], under solvent-free conditions in the presence of lemon juice as natural acid catalyst [239], in refluxing methanol and in the presence of a catalytic amount of nickel nitrate [240], and using phosphorus pentoxide/silica gel (P₂O₅/SiO₂) [241]. In addition, a green and efficient method for the synthesis of Schiff bases in aqueous media was described [242].

2.12.2. Mechanism

Concerning the mechanism of the transformation of aldehydes and amines into Schiff bases [90], two possible pathways are illustrated (Scheme 45 and Scheme 46) [239]. In Scheme 45, there is nucleophilic attack of a primary amine on carbonyl carbon that affords hydroxyl compound which on dehydration gives Schiff bases. The
formylation of Schiff bases 90 in this method largely depends on the rate of removal of water from the reaction mixture. Originally, the classical synthetic route for preparation of Schiff bases was reported by Schiff [243] which involves the condensation of primary amines with carbonyl compounds under azeotropic distillation [244] with the simultaneous removal of water. The removal of water during this condensation was conventionally facilitated by using molecular sieves [245] or a Dean-Stark apparatus [246]. In literature, the removal of water in situ has been accomplished by using dehydrating solvents such as tetramethyl orthosilicate [247] and trimethyl orthoformate [248].

To overcome the difficulties in the removal of water, an alternative method has been employed in which Lewis acid is used as a catalyst that accelerates nucleophilic attack of amines on carbonyl carbon as well as serving as a dehydrating agent for removal of water in the second step (Scheme 46). Several modified methods for synthesis of Schiff bases have been reported in literature in which Lewis acids were used as catalysts such as ZnCl2 [250], TiCl4 [251], alumina [252], P2O5 [253] and also by using hydrotalcite [254].

2.12.3. Reactivity of Schiff Bases

Schiff bases are important intermediates for the synthesis of many heterocyclic compounds. Condensation of 90 with indole in basic medium afforded N-substituted indoles 91 [255]-[258]. The thiazolidin-4-one derivatives 92a,b were obtained via reaction of 90 with thioglycolic [259]-[268] and thiolactic acids [269], respectively. Reaction of Schiff bases 90 with chloroacetyl chloride in dioxane and in the presence of triethylamine gave chloroacetamido derivatives 93 [266] or the azetidin-2-ones 94 [265] [270]. Similarly, reaction of 91 with phenylacetyl chloride in dioxane and in the presence of triethylamine produced the azetidinones 95 [271]. The pyrrol-2-one derivatives 96 can be synthesized by reaction of 90 with maleic anhydride [272]-[275] (Scheme 47).

2.13. Synthesis of Arylidene malononitrile Derivatives

The Knoevenagel reaction is the most simple and straightforward method used to produce the substituted alkenes [276]. Classically, the process consists of condensation of aldehydes or ketones with active methylene
compounds in the presence of a variety of reagents. Several bases [276]-[279], Lewis acids [280] [281] or heterogeneous media [282]-[289] were used as catalysts in Knoevenagel condensation reaction for the synthesis of arylidenemalononitriles 97. In addition, a simple and more efficient procedure was developed for the condensation of malononitrile with aromatic, heteroaromatic and aliphatic aldehydes in water [290] (Scheme 48).

Reactivity of Arylidenemalononitrile Derivatives
The arylidenemalononitriles 97 are useful intermediates for the synthesis of a variety of heterocyclic compounds, 2-aminobenzo[h]chromene-3-carbonitrile derivatives 98 were synthesized via condensation of 97 with α-naphthol in the presence of Mg/Al hydrotalcite under single-mode microwave irradiation [291] (Scheme 49). On the other hand, 3-aminobenzo[f]chromene derivatives 99 were obtained through condensation of 97 with β-naphthol [292] (Scheme 49). Pyrano[3,2-c]chromenes 100 were prepared by heating 4-hydroxycoumarin with 97 in pyridine [293], in ethanol and in the presence of triethylamine as a catalyst [294] or in water [295] (Scheme 49). Acid hydrolysis of pyrano[3,2-c]chromenes 100 produced compound 101, which is subsequently transformed into warfarin 102 (Ar = phenyl) [293] [296]-[298] (Scheme 50). Several pyrano[3,2-c]quinolines 103 were prepared via reaction of 4-hydroxyquinolin-2(1H)-ones with arylidenemalononitriles 97 [299] [300] (Scheme 49). Three component reaction between arylidenemalononitriles 97, 1,3-indanedione and thioglycolic acid under microwave irradiation afforded indeno[1,2-b]pyridine derivatives 104 [301] (Scheme 49). The analogous three-component reaction of 97 with 1,3-indanedione and 4-methylbenzenethiol, or aromatic amine under microwave irradiation afforded indeno[1,2-b]pyridines 105 [301] (Scheme 49). A series of dihydropyrrolo[1,2-f]phenanthridines 106 was prepared via reaction between 97, isocyanides and phenanthridine in dry diethyl ether [302]
Condensation of 97 with 5-methylresorcinol monohydrate in ethanol afforded the chromene derivatives 107 \[303\] (Scheme 49). Hexahydroquinolin-5-ones 108 were synthesized through reaction of 3-amino-cyclohex-2-en-1-ones with 97 \[304\] (Scheme 49). The thiazolopyridine derivatives 109 were obtained using 2:1 molar ratio of 97 and 2-(4,5-dihydro-4-oxothiazol-2-yl)acetonitrile or ethyl 2-(4,5-dihydro-4-oxothiazol-2-yl)acetate \[305\] \[306\] (Scheme 49). Reaction of 2-isoxazolin-5-ones with 97 was reported to yield pyrazolo[2,3-c]isoxazole derivatives 110 \[307\] (Scheme 49). Condensation of 97 with 3-methylpyrazol-5-ones gave the pyranopyrazole derivatives 111 \[292\] (Scheme 49). Whereas, pyrano[2,3-d]thiazole derivatives 112 were prepared through reaction of 97 with α-(4-oxothiazolin-2-yl)-α-phenylhydrazonoacetamide \[308\] \[309\] (Scheme 49). In addition, the pyrido[1,2-a]quinazoline derivatives 114 were synthesized via condensation of 97 with 2-(2-cyanoacetamido)benzoic acid \[309\] (Scheme 49). It was found that 3-phenyl-2-thiohydantoin reacts with 97 to give the corresponding pyrrolo[1,2-c]imidazole derivatives 115 \[310\] (Scheme 49). Reaction of 3-oxo-3-phenyl-N-(pyridin-3-yl)propanamide with 97 in ethanol gave tetrahydropyridines 116 \[311\] (Scheme 49). In addition, 6-acetyl-3-amino-2,5-diphenyl-2,3,4,5-tetrahydropyrazidine-4-carbonitrile derivatives 117 were obtained through reaction of 97 with 1-(phenylhydrazono)propan-2-one in pyridine \[312\].
(Scheme 49). Reaction of 97, ethyl acetoacetate and aqueous solution of ammonium hydroxide afforded 4H-pyran derivatives 118 [313] (Scheme 49). Tetrazoles 119 have been prepared through reaction of 97 with sodium azide in water [314] (Scheme 49). Michael additions of aryldienemalononitriles 97 with amidines in refluxing acetonitrile and in the presence of a catalytic amount of magnesium oxide produced the pyrimidine derivatives 120 [289] (Scheme 49). Reaction of 97 with hydrazide-hydrazene derivatives in dioxane and in the presence of triethylamine as a catalyst gave 6-amino-2-oxopyridine-3,5-dicarbonitriles 121 [315] (Scheme 49). The synthesis of thiophene derivatives 122 was accomplished through the condensation of 97 with thioglycolic acid [316] [317] (Scheme 49). 2-Amino-1,1,3-tricyanoprop-2-ene reacts with 97 to yield the pyridine derivatives 123 [318] [319] (Scheme 49). Treatment of 97 with thiourea in DMF and in the presence of a catalytic amount of piperidine resulted in the formation of the thioxopyrimidine derivatives 125 [321] (Scheme 49).

Reaction of aryldienemalononitriles 97 with 2-cyanothioacetamide in ethanol and in the presence of piperidine as a basic catalyst afforded 1,6-dihydro-6-thioxopyridine-2,3,5-tricarbonitriles 126. Reaction of thioxopyridines 126 with (2-acetoxyethoxy)methyl bromide in DMF in the presence of sodium hydride afforded 6-((2-acetoxyethoxy)methylthio)pyridine-2,3,5-tricarbonitriles 127 that is further reacted with ammonia in methanol to produce 6-((2-hydroxyethoxy)methylthio)pyridine-2,3,5-tricarbonitriles 128. Reaction of 126 with ethoxymethyl chloride in DMF and in the presence of sodium hydride gave 6-(ethoxymethylthio)pyridine-2,3,5-tricarbonitriles 129 [322] (Scheme 51).

It was reported that thermal Michael addition reaction takes place when 6,7-dimethoxyisochromanone 130 was treated with aryldienemalononitriles 97 at 190°C to afford 131 which underwent elimination of malononitrile producing 132 [323] (Scheme 52).


Diethyl aryldienemalonates 133 are easily accessible by Knoevenagel condensation [324] [325] (Scheme 53).
Various reaction conditions were reported for the preparation of diethyl arylidene malonates 133. The reaction was performed in water or ethanol without catalyst [326], in refluxing dry xylene and in the presence of a catalytic amount of piperidine/glacial acetic acid (3:1) [327], in refluxing ethanol and in the presence of a catalytic amount of piperidine/glacial acetic acid (2:1) [328] or in refluxing pyridine [329]. In addition, Knoevenagel condensations of benzaldehyde or substituted benzaldehydes with diethyl malonate was carried out in Lewis acidic 1-butyl-3-methylimidazolium chloroaluminate, [bmim]Cl∙xAlCl₃ and 1-butylpyridinium chloroaluminate,
[bpy]Cl\cdot xAlCl₃ ionic liquids [330].

Reactivity of Diethyl Arylidene Malonate Derivatives
Reaction of diethyl arylidene malonates 133 with indole 134 in isobutanol at room temperature, employing Cu(OTf)₂-bis(oxazoline) complexes under nitrogen afforded ethyl 3-aryl-2-ethoxycarbonyl-3-(3-indolyl) propanoates 135 [331] (Scheme 54). Reaction of diethyl 4-methoxybenzylidene malonate 136 with but-2-yne-1,4-diol 137 in the presence of sodium hydride (NaH) in THF at room temperature for five minutes afforded ethyl 3-(4-methoxyphenyl)-4-oxo-3a,4,6-tetrahydro-1H-furo[3,4-c]pyran-3a-carboxylate 138 [332]-[335] (Scheme 55).

2.15. Synthesis of Ethyl Arylidene Cyanoacetate Derivatives
Ethyl arylidene cyanoacetates 139 are prepared via Knoevenagel condensation of aldehydes with ethyl cyanoacetate (Scheme 56). Several publications were reported for the synthesis of ethyl arylidene cyanoacetates. The reaction was carried out in aqueous medium at room temperature [336], in refluxing ethanol and in the presence of piperidine/glacial acetic acid (2:1) [328], in refluxing ethanol and in the presence of Trizma [337]. Also, this condensation was performed in ethanol/water mixture and in the presence of sodium or potassium hydroxide at 50°C - 60°C [279]. The same reaction was carried out using magnesium bromide diethyl etherate (MgBr₂·OEt₂) as Lewis acid in the presence of triethylamine [338]. In addition, poly(4-methyl vinylpyridinium) hydroxide/SBA-15, a novel basic polymeric composite was applied as a recyclable catalyst for the Knoevenagel condensation reaction of aromatic aldehydes with ethyl cyanoacetate in water at 95°C [339]. Furthermore, they were prepared via heating a mixture of aldehyde and ethyl cyanoacetate at 80°C - 85°C in an oil bath and in the presence of rare earth triflates as Yb(OTf)₃ [340]. The same reaction was performed in distilled water and in the presence of hydroxyapatite supported caesium carbonate as a recyclable solid base catalyst (HAP-Cs₂CO₃) [278] or under microwave irradiation [341].

Reactivity of Ethyl Arylidene Cyanoacetate Derivatives
The thiazolopyridine derivatives 109 were also obtained using 2:1 molar ratio of ethyl arylidene cyanoacetates 139 and 2-(4,5-dihydro-4-oxothiazol-2-yl)acetonitrile or ethyl 2-(4,5-dihydro-4-oxothiazol-2-yl)acetate [305] [306] (Scheme 57). Reaction of ethyl arylidene cyanoacetates 139 with hydrazide-hydrazone derivatives in dioxane and in the presence of a catalytic amount of triethylamine produced ethyl 2-amino-5-cyano-6-oxopyridine-3-carboxylates 140 [298] (Scheme 57). The synthesis of thiophene derivatives 141 was accomplished through the condensation of 139 with thioglycolic acid [316] [317] (Scheme 57). Reaction of 139 with 2-cyanoacetic

![Scheme 54. Preparation of compounds 135.](image)

![Scheme 55. Preparation of compounds 138.](image)

![Scheme 56. Preparation of compounds 139.](image)
Scheme 57. Preparation of compounds 109 and 140-147.
acid hydrazide gave the pyridine derivatives 142 [342] (Scheme 57). The reaction of 139 with \( S \)-methylthiourea in pyridine produced the pyrimidine derivatives 143 [343]. In addition, the pyrido[1,2-\( \alpha \)]quinazoline derivatives 144 were synthesized via condensation of 139 with 2-(2-cyanoacetamido)benzoic acid [309] (Scheme 57). Moreover, the pyrano[2,3-c]pyrazole derivatives 145 were obtained through condensation of 139 with 3-methylpyrazolone derivatives [344] [345] (Scheme 57). Condensation of 139 with barbituric or thiobarbituric acids afforded the corresponding pyrano[3,2-\( d \)]pyrimidine derivatives 146 [308] (Scheme 57). Whereas, pyrano[2,3-\( d \)]thiazole derivatives 147 were prepared through reaction of 139 with \( \alpha \)-(4-oxothiazolin-2-yl)-\( \alpha \)-phenylhydrazonoacetamide [308] (Scheme 57).

Reaction of 139 with 2-cyanothioacetamide in ethanol and in the presence of a catalytic amount of piperidine afforded ethyl 3,5-dicyano-1,6-dihydro-6-thioxopyridine-2-carboxylates 148. Reaction of 6-thioxopyridines 148 with (2-acetoxyethoxy)methyl bromide in DMF and in the presence of sodium hydride afforded ethyl 3,5-dicyano-6-[2-acetoxyethoxy)methylthio]pyridine-2-carboxylates 149 that is further reacted with ammonia in methanol to produce ethyl 3,5-dicyano-6-[2-hydroxyethoxy)methylthio]pyridine-2-carboxylates 150. Reaction of 148 with ethoxymethyl chloride in DMF and in the presence of sodium hydride gave ethyl 3,5-dicyano-6-(ethoxymethylthio)pyridine-2-carboxylates 151 [322] (Scheme 58).

2.16. Synthesis of Arylidenecyanoacetamide Derivatives

Arylidenecyanoacetamides 152 are prepared via Knoevenagel condensation of aldehydes with cyanoacetamide derivatives (Scheme 59). The reaction was carried out under solvent-free conditions [346], in water and in the presence of triethylbenzylammonium chloride (TEBA) [347], in aqueous medium at room temperature [326], or via grinding of aldehydes with cyanoacetamide derivatives at room temperature and in the presence of a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [348].

Reactivity of Arylidenecyanoacetamides

The benzylidenecyanoacetamide derivative 153 has been extensively utilized in heterocyclic synthesis. Reaction of 153 with hydrazine hydrate or phenylhydrazine in refluxing ethanol and in the presence of a catalytic amount of piperidine produced the pyrazole derivatives 154 [349]. The 2-oxopyrimidine derivative 155 was prepared through condensation of 153 with urea in refluxing ethanol and in the presence of a catalytic amount of piperidine (Scheme 60) [349]. In addition, the 2-thioxopyrimidine derivative 156 was obtained through...
condensation of 153 with thiosemicarbazide in refluxing ethanol and in the presence of a catalytic amount of piperidine (Scheme 60) [349]. Moreover, reaction of 153 with cyanoacetamide, cyanothioacetamide or cyanoacetic acid hydrazide afforded the cyanopyridine derivatives 157 (Scheme 60) [349].

### 2.17. Synthesis of 5-Arylidene Derivatives of Barbituric and Thiobarbituric Acids

Barbituric and thiobarbituric acids have attracted the attention of medicinal chemists for over hundred years due to their therapeutic values [350] [351]. 5-Arylidenebarbiturate/thiobarbiturate derivatives are important members of the pyrimidine family. The major importance of these compounds has been centered on their application as useful precursors in the preparation of new heterocyclic compounds [293] and as selective oxidizing agents [352]-[354]. Barbituric acid and its derivatives exhibited different biological activities such as antibacterial, hypotensive and tranquilizing activities [355]. The clinical use of barbiturates in neurological disorders has also been investigated [356]. 5-Arylidenebarbiturates/thiobarbiturates 158 (Scheme 61) have been synthesized by Knoevenagel reaction of barbituric acid with different aldehydes under various conditions. The reaction was carried out under aqueous reflux using acetic acid as a catalyst [357]. Villemin and Labiad [358] synthesized 5-arylidenebarbiturates under microwave irradiation and in the presence of montmorillonite KSF clay. Dewan and Singh [359] reported various catalysts like NH₄OAc/AcOH, montmorillonite K-10, silica gel, basic alumina, NaCl, montmorillonite KSF, and KSF/NaCl for the synthesis of 5-arylidenebarbiturates/thiobarbiturates 158. A grinding method has also been employed for the synthesis of 158 [360]. The same reaction was promoted by
infrared irradiation in absence of solvent [361]. Also, it was carried out on basic alumina in a conventional microwave oven in the absence of solvent [362]. In addition, the same reaction has been achieved by employing bismuth chloride under solvent-free conditions [363]. Reddy et al. [364] reported the same reaction under microwave irradiation in absence of solvent and catalyst. In addition, Khan et al. [365] reported an improved, rapid and convenient method under eco-benign conditions i.e., using water as a solvent and bismuth chloride as a catalyst at room temperature. Recently, 5-arylidenebarbiturate/thiobarbiturate derivatives 158 were obtained in excellent yields and high purity through condensation of barbituric or thiobarbituric acid with aromatic aldehydes in distilled water at room temperature and in the presence of a catalytic amount of ethanolamine [366] or L-tyrosine [367].

**Reactivity of Arylidenebarbiturates and Thiobarbiturates**

Reaction of 158 with malononitrile in ethanol and in the presence of a catalytic amount of piperidine afforded 7-amino-5-aryl-2-oxo(thioxo)-4-oxo-2,3,4,5-tetrahydro-1H-pyran[2,3-d]pyrimidine-6-carbonitriles 159 [366] (Scheme 62). Cycloaddition reactions of 5-arylidenebarbiturate derivatives 158 with a tenfold excess of ethyl vinyl ether in methylene chloride at room temperature afforded 2H-pyran[2,3-d]pyrimidine-2,4-(3H)-diones 160 [368] (Scheme 63).

### 2.18. Synthesis of Arylidene Derivatives of Meldrum’s Acid

2,2-Dimethyl-1,3-dioxane-4,6-dione (Meldrum’s acid) undergoes standard Knoevenagel condensation with aromatic and heteroaromatic aldehydes furnishing the corresponding arylidene derivatives 161 (Scheme 64), which are versatile substrates for different kinds of reactions [369]. In addition, they are useful intermediates for cycloaddition reaction and for the synthesis of heterocyclic compounds with potential pharmacological activity [370]. The Knoevenagel condensation of aldehydes with Meldrum’s acid is generally catalyzed by bases, such as pyridine [371] or by piperidine/glacial acetic acid in benzene [372]. Uncatalyzed reaction was reported in literature using DMF or DMSO as solvent [373]. In addition, anhydrous zinc chloride was reported to promote the reaction in absence of any solvent [374]. The same reaction was also carried out in water [375]. In addition, the Knoevenagel condensation of aromatic aldehydes with Meldrum’s acid proceeded efficiently in the recyclable
ionic liquid [bmim]BF$_4$ at room temperature and in the presence of a catalytic amount of piperidine [376]. Also, the same condensation was carried out in methanol at room temperature [377].

**Reactivity of Arylidene Derivatives of Meldrum’s Acid**

The epoxide analogues of arylidene Meldrum’s acid 162 were prepared through reaction of 161 with hydrogen peroxide in acetonitrile at room temperature [378] [379] (Scheme 65).

Rhodium-catalyzed additions of arylboron reagents to 161 in dioxane at room temperature gave compounds 163 [380] (Scheme 66). The condensation of 161 with 3-amino-1,2,4-triazole in nitrobenzene afforded 4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-$a$]pyrimidin-5-ones 164. In DMF, the reaction proceeds with the formation of arylsubstituted $N$-(2$H$,1,2,4-triazol-3-yl)-3-(2$H$,1,2,4-triazol-3-ylamino)propionamides 165, in addition, the amide 166 and the aldehydes were present in the reaction mixture [381] (Scheme 67).
2.19. Synthesis of 2-Arylidene Dimedone and Bisdimedone Derivatives

5,5-Dimethylcyclohexane-1,3-dione (dimedone) was condensed with aromatic aldehydes in equimolar ratio and in presence of bases such as potassium hydroxide [382] [383] or piperidine [383] to give 2-arylidene-5,5-dimethylcyclohexane-1,3-dione derivatives 167 (Scheme 68). The same products were obtained through fusion of equimolar amounts of the aromatic aldehydes and dimedone in an oil bath at 150°C [384]. On the other hand, reaction of dimedone with aromatic aldehydes in 2:1 molar ratio afforded the bisdimedone derivatives 168 (Scheme 68), several reaction conditions were reported for this reaction. The reaction was performed in refluxing aqueous ethanol and in the presence of a catalytic amount of piperidine [385], under solvent-free conditions [346], in aqueous ethanol at room temperature and in the presence of a catalytic amount of piperidine [386], in water at 100°C and in the presence of a catalytic amount of iodine [387], HClO₄-SiO₂ or PPA-SiO₂ [388], in refluxing aqueous methanol [389], in aqueous media at room temperature [390] or in refluxing acetonitrile and in the presence of of zinc oxide as a catalyst [391], also it was carried out in dry methylene chloride and in the presence of silica chloride nano particle (nano SiO₂-Cl) [392] to afford the corresponding 2,2′-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one) (bisdimedone derivatives) 168. The same reaction was performed using ytterbium triflate [Yb(OTf)₃-SiO₂] and amine as a catalytic system under solvent-free conditions.

![Scheme 68. Preparation of compounds 167 and 168.](image1)

![Scheme 69. Preparation of compounds 169.](image2)

![Scheme 70. Preparation of compounds 170-172.](image3)
This method is advantageous as being eco-friendly, non-corrosive, and allows reutilization of the catalytic system. Recently, bisdimedone derivatives 168 were obtained through reaction of dimedone with aromatic aldehydes in 2:1 molar ratio in ethylene glycol and in presence of nickel nanoparticles [394].

**Reactivity of 2-Arylidene Dimedone and Bisdimedone Derivatives**

Reaction of arylidenedimedone derivatives 167 with \(N\)-benzyl-\(N\)-phenylhydrazine in 50% acetic acid produced compounds 169 [384] (Scheme 69).

When bisdimedone derivatives 168 were reacted with different amines in ethanol and in the presence of a catalytic amount of \(\text{P}_2\text{O}_5\), \(10\)-(substituted phenyl)-3,4,6,7,9,10-hexahydro-1,8(2\(H\), 5\(H\))-acridinedione derivatives 170 were obtained. The condensation of \(N\)-(2-aminoethyl)piperazine with bisdimedones 168 in acetic acid afforded the acridinediones 171 in which the \(N\)-acetylation of the piperazine ring has also occurred. The reaction of bisdimedones 168 with thiosemicarbazide gave \(N\)-(3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-1,8-dioxo-(2\(H\), 5\(H\))-acridin-10-yl)thiourea derivatives 172 [395] (Scheme 70).

**3. Conclusion**

Literature data have been summarized to help chemists to find information appropriate for the high synthetic potential of different arylidene derivatives. Syntheses of many biologically active heterocyclic compounds belonging to these compounds have also been reported.

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Efficient and Eco-Friendly Catalyst in Aqueous Medium.


5-Arylidene-pyrimidine-2,4,6-triones and 5-Arylidene-2-thioxo-dihydro-pyrimidine-4,6-diones Using L-Tyrosine as an Efficient and Eco-Friendly Catalyst in Aqueous Medium.

http://dx.doi.org/10.7598/cst2013.385

5-Arylidene-2-thioxo-dihydro-pyrimidine-4,6-diones Using L-Tyrosine as an Efficient and Eco-Friendly Catalyst in Aqueous Medium.

http://dx.doi.org/10.1016/j.tetlet.2009.03.188

Facile and Green Syntheses of Arylidene-pyrimidine-2,4,6-triones and 5-Arylidene-2-thioxo-dihydro-pyrimidine-4,6-diones Using L-Tyrosine as an Efficient and Eco-Friendly Catalyst in Aqueous Medium.

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